Connectome based classification of BDNF Met allele carriers

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What is BDNF?

Brain-derived neurotrophic factor

➔ Protein essential for brain development & long term potentiation

Patterson SL, 1996, *Neuron*

Associated gene, BDNF

- Regulates the activity-dependent release of the BDNF protein

Egan MF, 2003, *Cell*

- Alleles: **G** encodes *Valine*, **A** encodes *Methionine*
- Common single-nucleotide polymorphism (SNP):

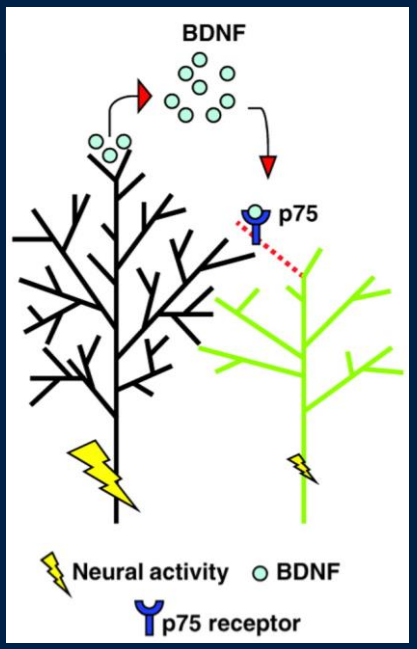
  Val66Met = swap Val for Met at codon 6,6

So What?

- Carrying MET allele
  - ➔ reduced BDNF activity-dependent secretion in the brain

Egan MF, 2003, *Cell*

- BDNF role
  - ➔ pruning of silent axonal branches during brain development



Singh KK, 2008, *Nat Neurosci*
Cao L, 2007, *Curr Biol*

Study Data

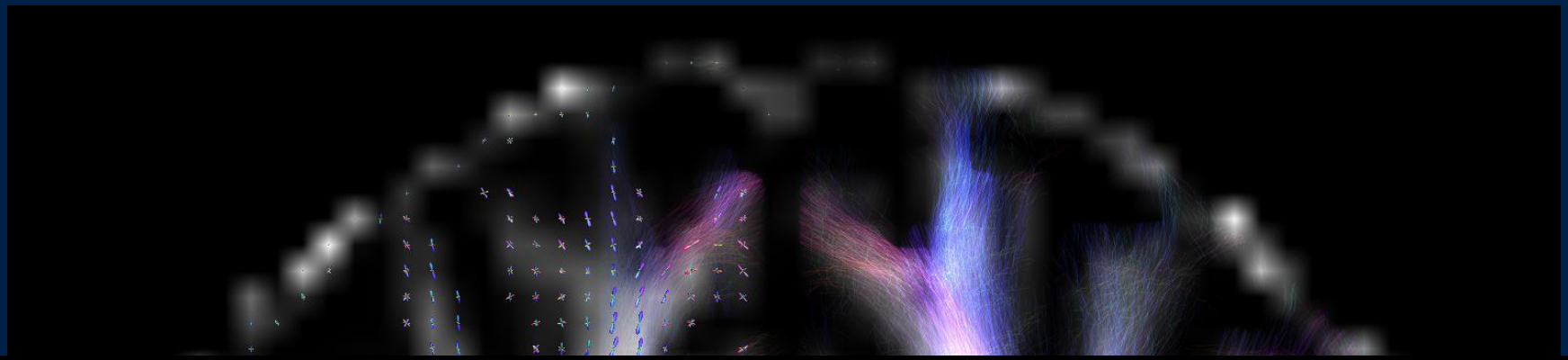
- Population (n=36)
  - 15 Met carriers, 21 Val homozygotes
  - Highly regulated young healthy subjects (18-25y)
- MR acquisition
  - High-resolution T1 MPRAGE (1mm^3 isotropic voxels)
  - Diffusion-weighted MRI
    - 7 unweighted (b=100) images
    - 61 directional (b=1000) images
    - 2.3 x 2.3 x 2.3 mm^3 isotropic voxels

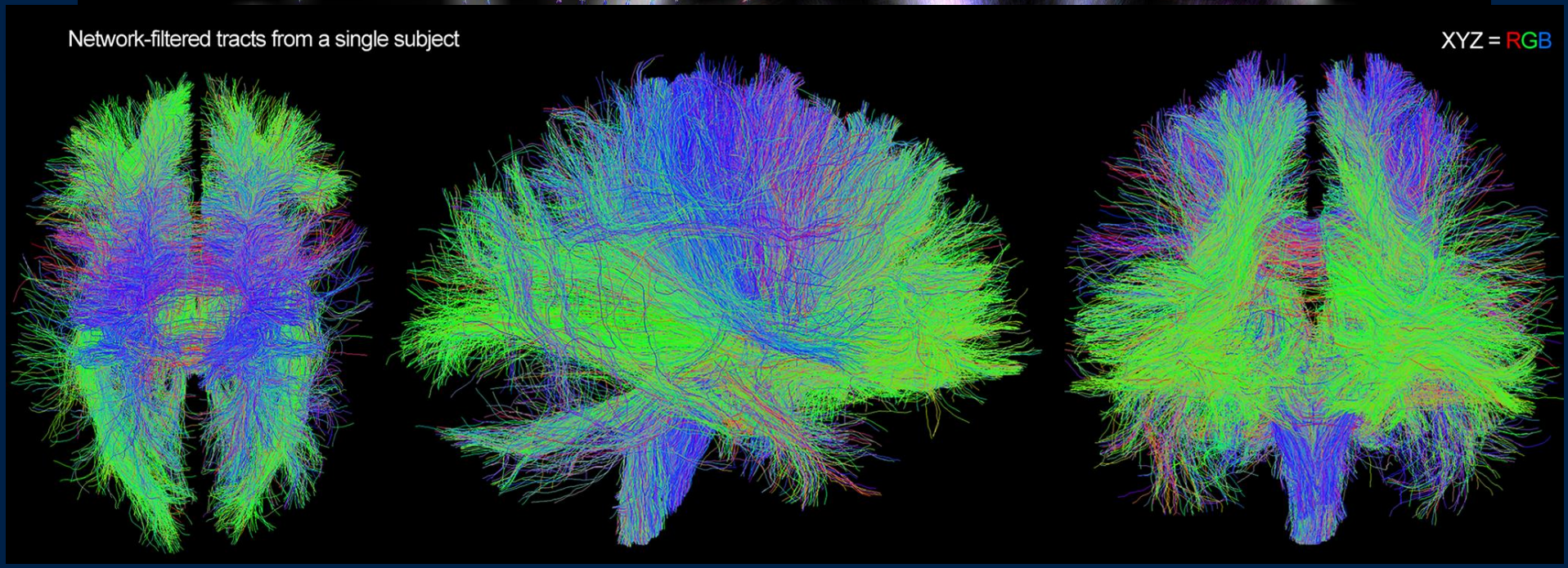
Connectome Mapping

- Probabilistic Tractography
  - Spherical deconvolution → ODFs
  - 300,000 fibers, randomly seeded in WM

Tournier JD, 2004 & 2007, *Neuroimage*

Connectome Mapping





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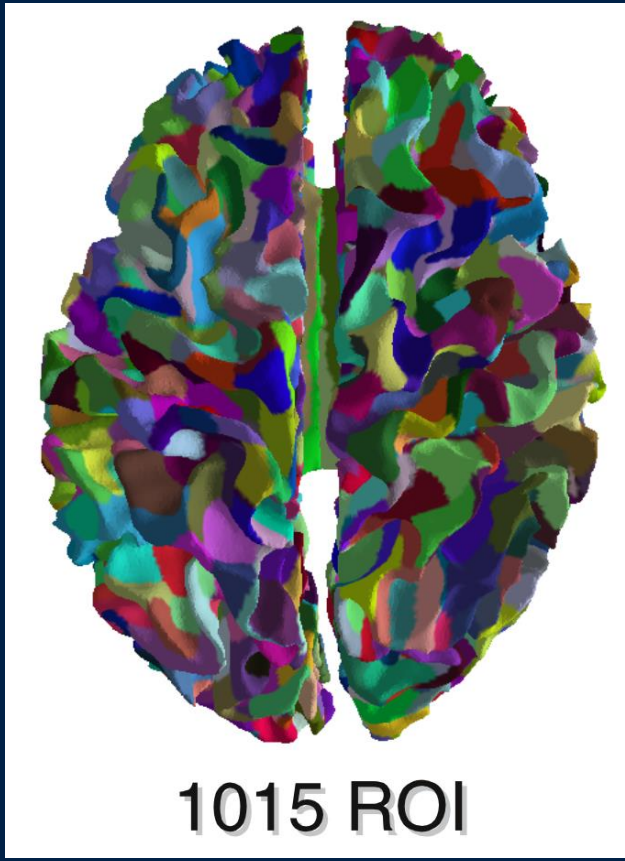
- Anatomical segmentation & parcellation
  - Desikan-Killiany atlas (83 regions)
  - Lausanne 1015-region atlas

Desikan RS, 2006, *Neuroimage*
Hagmann P, 2008, *PLoS Biol*
Daducci A, 2012, *PLoS One*

Connectome Mapping



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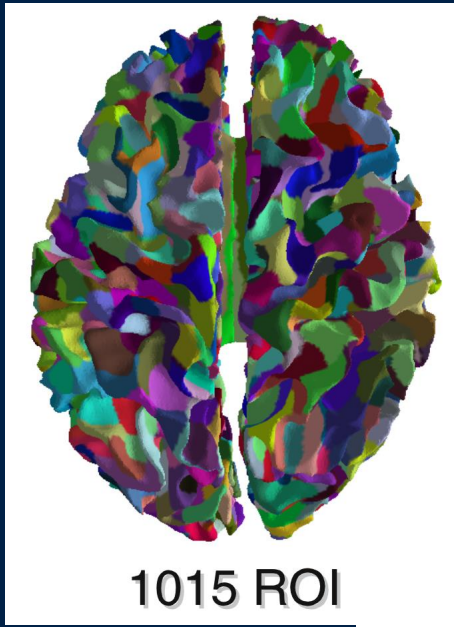
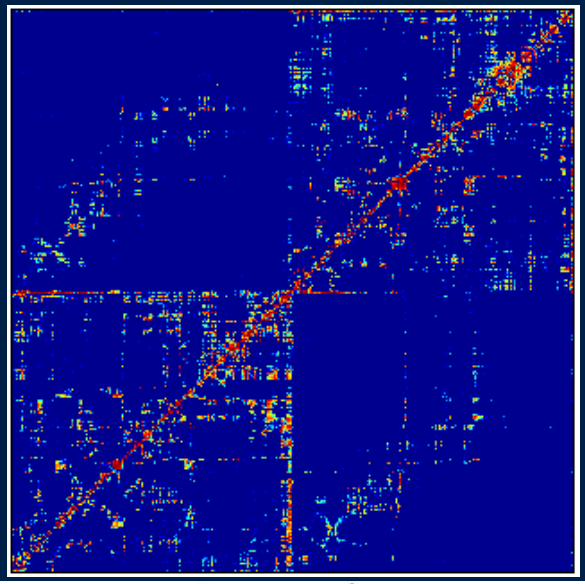
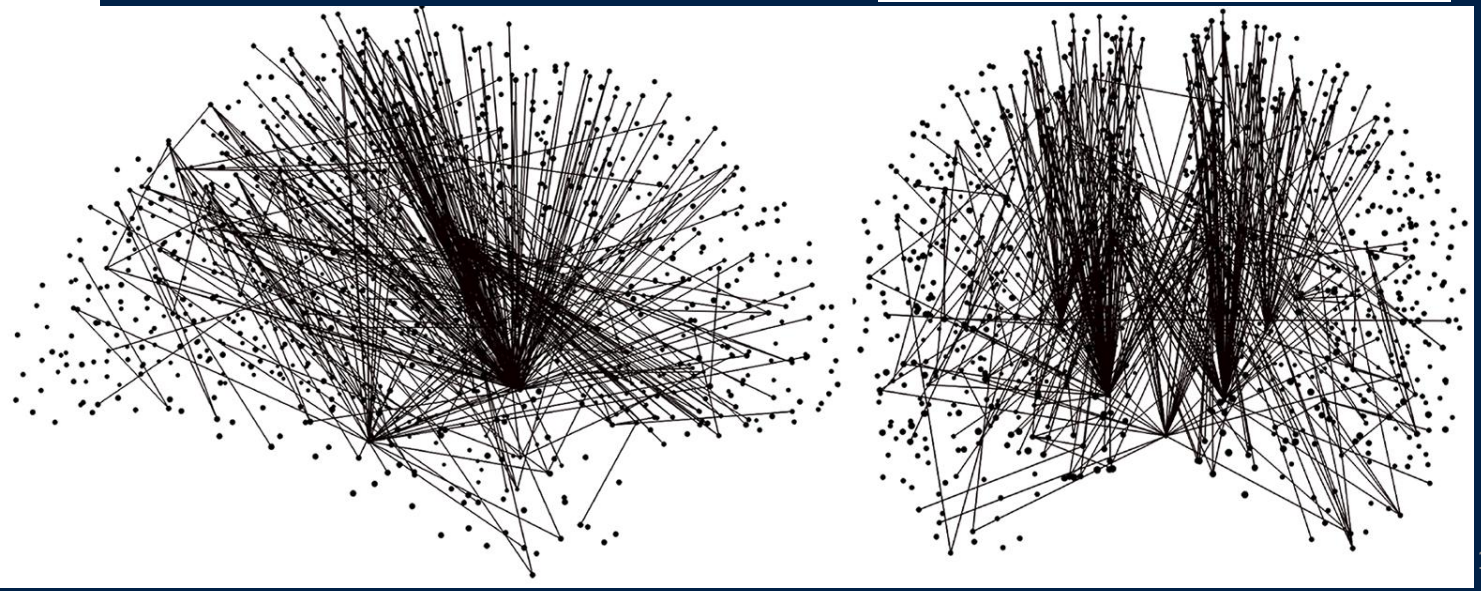
- Connectome = 1015 x 1015 matrix
  - 1 fiber crossing 2 regions → +1 connection

Connectome Mapping







Statistical analysis

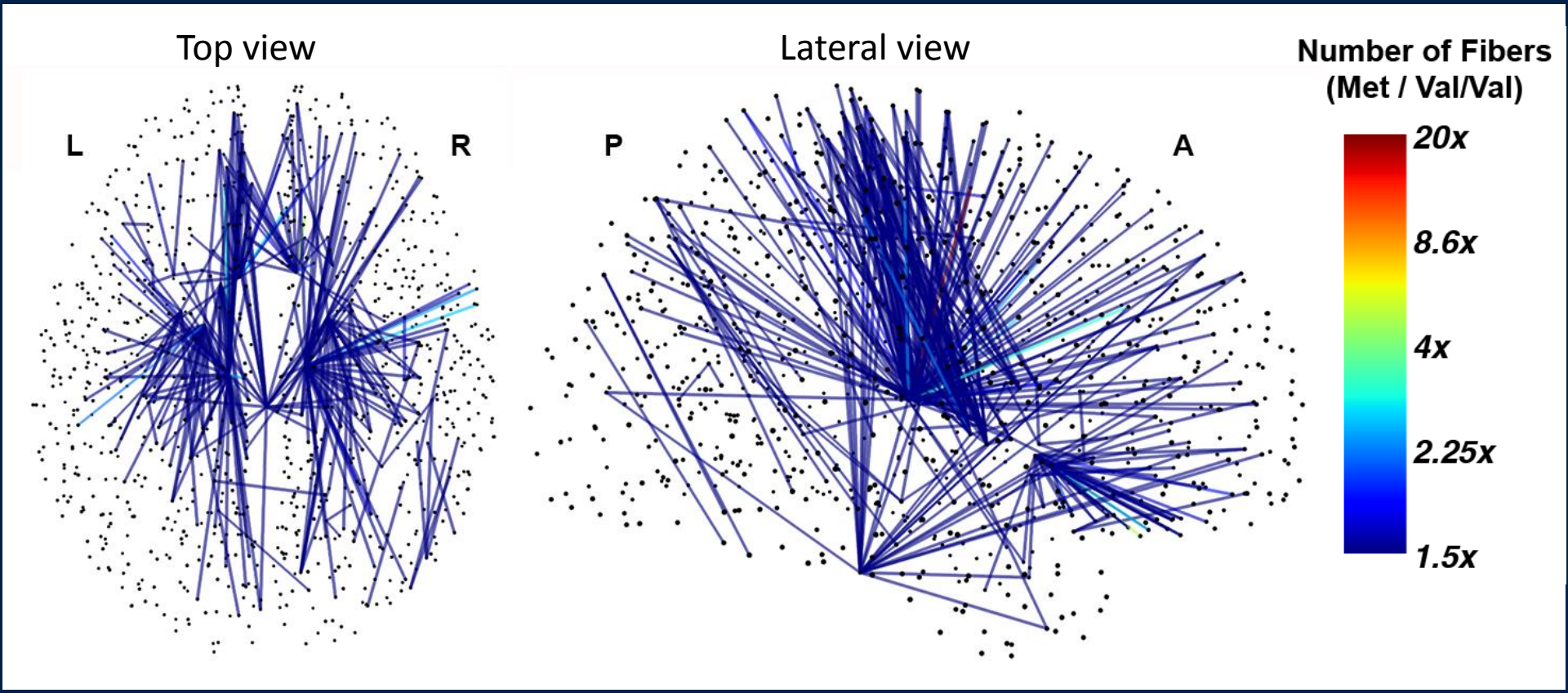
Compare connectivity matrices with

- Network-based statistics (NBS)
  - Non-parametric test using NBS

Zalesky A, 2010, *Neuroimage*

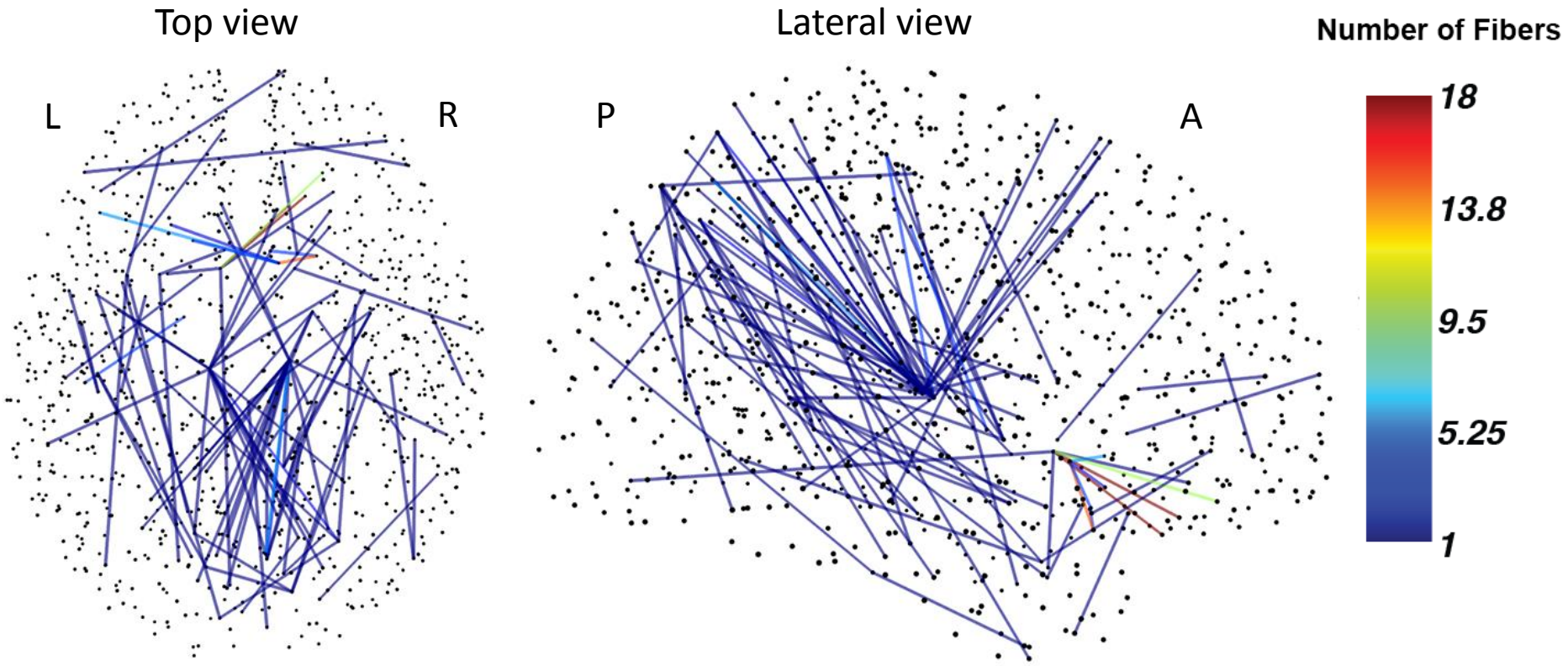
NBS Results

Increased fibers in Met carriers



NBS Results

Fibers not present in Val homozygotes



NBS Results

- Some connections only in Met carriers
- Increased connection strength in Met carriers:
  - between bilateral thalami and brainstem
  - sensorimotor areas of parietal and frontal cortex
  - ventromedial prefrontal cortex (anterior forceps)
  - occipital, posterior parietal, and temporal areas also differ to a lesser extent.

Statistical analysis

Compare connectivity matrices with

- Network-based statistics (NBS)
  - Non-parametric test using NBS

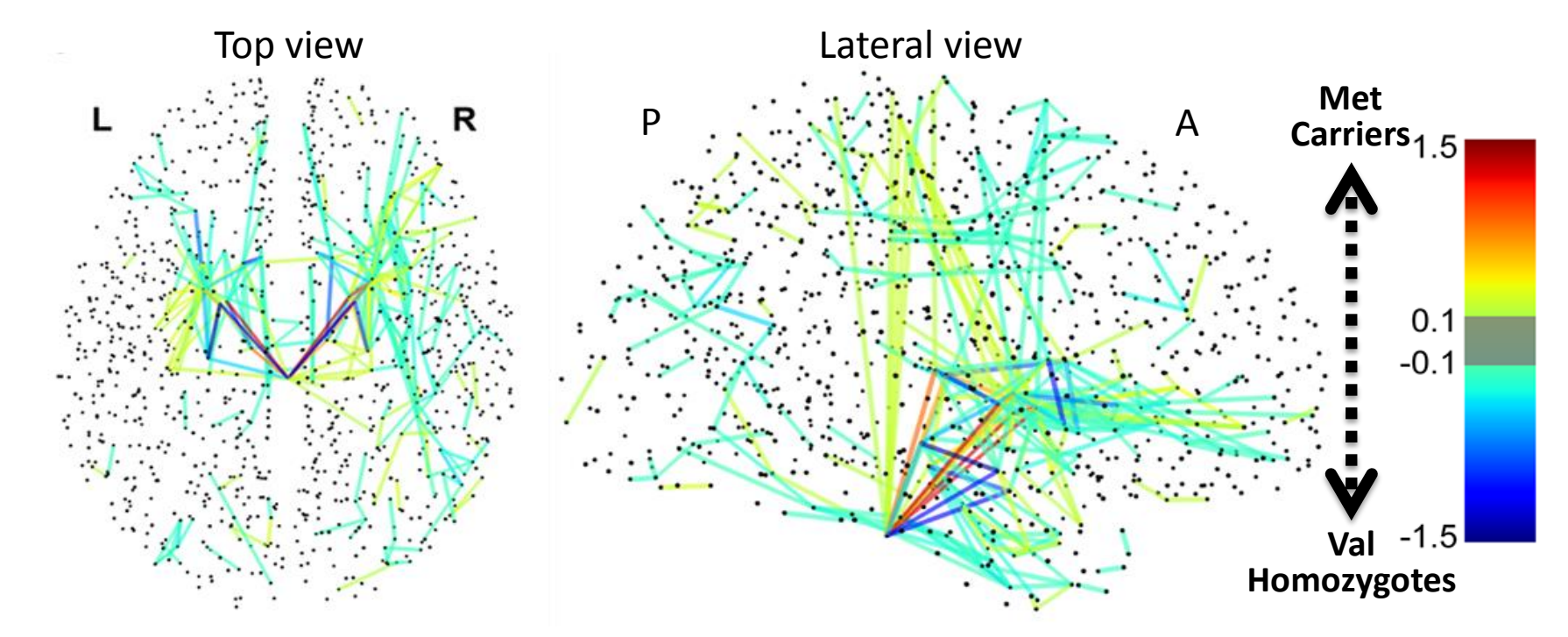
Zalesky A, 2010, *Neuroimage*

- Multivariate statistics
  - Gaussian Processes classification
  - Leave-one-out cross-validation procedure
  - Permutation testing

Rasmussen CE, 2006
Schrouff J, 2013, *Neuroinformatics*

Classification Results

- Balanced accuracy: 87.1% (p<.001)
- Class predictive values (ValVal & Met-carrier): 94.4% & 77.8%



Classification Results

Grouping according to

- adenosine deaminase (ADA) genotype:

  Classification of G/A (n=16) vs. G/G (n=20)

  ➔ accuracy 58.3% (n.s.)

- gender:

  Classification of male (n=18) vs. female (n=18)

  ➔ accuracy 63.9% (n.s.)

No significant classification for ADA nor gender!

Discussion

- *BDNF* Met carriers prune less axons during brain development
- Resulting tracts stay in the brain
  - Seem to provide little or no benefit at young age
  - May protect against age-related deficits

Harris SE, 2006, *Mol Psychiatry*
Gajewski PD, 2011, *Neurobiol Aging*

- Extraneous tracts are found as increases in fractional anisotropy

Chiang MC, 2011a and 2011b, *Neuroimage*

Conclusions

- *BDNF* genotype (allelic group) can be predicted based on brain connectivity
- Longitudinal *BDNF* studies are needed to cover youth-adult brain development
- Differences between Val66Met and Met66Met polymorphisms should be examined

Acknowledgments

Open-source software:

- Nipype/Nibabel/Dipy http://nipy.org
- Mrtrix http://www.brain.org.au/software/mrtrix/
- ConnectomeViewer http://cmtk.org
- PRoNTo http://www.mlnl.cs.ucl.ac.uk/pronto/

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Poster #3840, Wednesday 13:30-15:30.

Paper recently accepted in PLOS ONE.

Thank you for your attention!